Criteria for HNF1B analysis in patients with congenital abnormalities of kidney and urinary tract

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ABSTRACT

BACKGROUND AND OBJECTIVS:

Congenital anomalies of kidneys and urinary tract (CAKUT) are the most predominant developmental disorders comprising ≈20-30% of all anomalies identified in the prenatal period. Mutations in hepatocyte nuclear factor 1-beta (HNF1B) involved in the development of kidneys, liver, pancreas and urogenital tract are the most frequent monogenetic cause of CAKUT found in approximately 10-30% of the patients depending on screening policy and study design. We aimed to define criteria for analysis of *HNF1B* in a prospective cohort of CAKUT patients.

DESIGN, SETTING, PARTICIPANTS AND MEASUREMENTS

We included CAKUT patients diagnosed in our paediatric and adult nephrology departments from January 2013 until April 2013 bases on predefined screening criteria. Subjects presenting with at least one major renal criterion or one minor renal criterion with one or more extra-renal criteria in the personal or familial history were considered eligible.

RESULTS

We prospectively screened 205 patients and detected *HNF1B* mutations in 10% (n=20, 12 children, median age 4.2 (range 0-13.1) and 8 adults (median age 34.8 (range 16.6-62) years). We observed that bilateral renal anomaly, renal cysts from unknown origin, a combination of two major renal criteria, and hypomagnesaemia were predictive for finding *HNF1B* abnormalities ($p<0.001$; $p<0.001$; $p=0.004$; $p=0.008$ respectively).

CONCLUSIONS

We demonstrated that *HNF1B* mutations are responsible for ≈10% of CAKUT cases, both in children and in adults. Based on our results we propose adapted criteria for *HNF1B* analysis to reduce the screening costs without missing affected patients. These criteria should be reaffirmed in a larger validation cohort.

KEYWORDS

CAKUT, genetic screening, hepatocyte nuclear factor 1-beta, HNF1B, renal development

ABBREVIATIONS

CAKUT	congenital anomalies of kidney and urinary tract
HNF1B	hepatocyte nuclear factor 1-beta
TCF2	transcription factor 2
MODY	maturity onset diabetes of the young
RCAD	renal cysts and diabetes syndrome
VUR	vesico-uretral reflux
MCDK	multicystic dysplastic kidney

INTRODUCTION

Congenital anomalies of kidneys and urinary tract (CAKUT) are the most frequent developmental disorders in humans and remain the leading cause of chronic kidney disease in childhood [1]. The aetiology of CAKUT is heterogeneous and involves genetic, epigenetic and environmental factors [2, 3]. A multitude of monogenetic disorders have been identified in CAKUT cases with mutations in the hepatocyte nuclear factor 1 beta (*HNF-1β*) being currently the most frequently reported underlying genetic cause [3].

HNF-1β belongs to the homeodomain-containing family of transcription factors encoded by the transcription factor 2 (*TCF2* or *HNF1B*) gene located on chromosome 17 and is involved in the organogenesis of kidneys, urinary tract, liver and pancreas. HNF-1β functions as a homodimer or a heterodimer with structurally related HNF-1α [4]. While mutations in HNF-1α are the most frequent genetic cause of the maturity onset diabetes of the young (MODY) [5], renal malformations (CAKUT) are specific for HNF-1β [5] and can occur either in combination with MODY (coined as renal cysts and diabetes syndrome, RCAD or MODY5), liver disease, hyperuricemia, pancreas atrophy or be isolated [6]. Although the *HNF1B*-associated disorders are characterized by an autosomal dominant inheritance, there is a high heterogeneity in phenotype, even between individuals with the same inherited mutation [7-9]. Therefore, selection criteria for *HNF1B* genetic analysis are not well defined and the percentage of *HNF1B* mutations in patients with CAKUT varies largely between 10 and 30% depending on screening policy and study design [8, 10, 11]. Retrospective studies and inclusion of more family members might probably increase this percentage.

Renal manifestations are observed in almost all patients with *HNF1B* mutations and encompass a spectrum of abnormalities either isolated or in combination with extra-renal manifestations (Table 1) [8-10, 12-15].

In this study we aimed to test published criteria for analysis of *HNF1B* in a prospective single centre cohort of incident paediatric and adult patients with CAKUT. Based on these results we propose adapted criteria for *HNF1B* analysis, which might reduce the screening costs without missing affected patients.

MATERIALS AND METHODS

Patients

We prospectively included CAKUT patients from the paediatric and adult nephrology department from January 2010 until April 2013 having at least one major renal anomaly (fetal bilateral hyperechogenic kidneys, multicystic dysplastic kidney (MCDK), renal agenesis, hypoplastic or dysplastic kidneys, cysts of unknown origin) or one minor renal (ectopic kidney, vesico-ureteral reflux (VUR), hydronephrosis) combined with one or more extra-renal anomalies associated with *HNF1B* mutations (MODY, hypomagnesaemia, liver function anomalies) in the personal history or a familial history of renal or extra-renal manifestations (Table 1).

The diagnosis of CAKUT was made by renal ultrasound (US) in all patients; micturating cystourethrogram or nuclear scans were considered in the diagnosis if applicable. Antenatal diagnosis of CAKUT was made in 85/147 of the children and in 1/58 adults. Two hundred and five patients (147 <16 years old and 58 >16 years old; 120 males) were included in final analysis.

Biochemical investigations

We analysed electrolytes, creatinine, albumin, glucose and liver enzymes in serum/plasma and urine electrolytes, glucose, protein and creatinine by routine laboratory procedures. Hyperuricemia was defined as >5.7 mmol/l in females and >7 mmol/l in males, hypomagnesaemia was defined as <0.6 mmol/l and corrected for age, hypokalemia was defined as <3.5 mmol/l. Creatinine clearance was calculated using Schwartz equation for children [16] and Cockcroft-Gault formula for adults [17].

Genetic analysis

DNA was isolated from blood samples using standard methods. Primers were designed to cover all coding exons of the *HNF1B* gene (NM_000458.2), including exon–intron boundaries. Primer sequences are available on request. 75 ng of genomic DNA was amplified using Taq DNA polymerase (Roche) in a total volume of 25 µl. Amplification was performed by initial denaturation at 95°C for 15 minutes, followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 56°C for 45 seconds, extension at 72°C for 45 seconds, and a final extension at 72°C for 5 minutes. After PCR amplification, the samples were purified,

directly sequenced and analysed according to the ABI BigDye Terminator Cycle Sequencing protocol and the automatic genetic analyser ABI3730xl (Applied Biosystems). Results were analysed using SeqPilot (JCI Medical Systems).

Deletions and duplications were analysed using the multiplex ligation probe amplification (MLPA) assay MODY P241 kit (MRC-Holland). This kit includes probes for all nine exons of *HNF1B*. Fragment analysis was carried out using standard methods on the genetic analyzer ABI3730xl (Applied Biosystems). Results were analysed using Genemarker Software (Softgenetics).

Stop- and splice mutations are considered pathogenic; missense mutations were considered significant if either they were reported in the literature in association with the pathological phenotype (Human Gene Mutation Database, HGMD) or in case of *de* novo variants, if there was a change in an amino acid of HNF1 β and segregation analysis showed the absence of this variant in healthy family members and/or based on phylogenetic conservation predictions (SIFT, Polyphen2, Mutation Taster).

Ethics

This study has been approved by the local ethical committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All patients (or legal custodians in case of children under 16) gave their informed consent prior to their inclusion in the study and children gave informed assent if possible.

Statistical analysis

Contingency tables were calculated for the *HNF1B* groups with predictive variables to test bivariate frequency distributions. We used Fisher's Exact test for 2x2 tables and Fisher-Freeman-Halton Exact test for all other table formats in case of low expected counts (<5) and Pearson Chi-square tests otherwise. If a significant difference in frequency distribution was found, we made pair wise comparisons for each of the categories of the predictive variables using a z-test with Bonferroni correction (α=0.05). Additionally, we used continuous predictive variables that were first tested against the null hypothesis of normal distribution using Shapiro Wilk test (α=0.05). If disproved, the non-parametric Mann-Whitney U test was used to compare the mean scores of the two groups. If approved the equality of variance of both groups

was assessed using Levene's test (α=0.05) and based on the result the appropriate value of the Student's t-test was calculated (α=0.05). Variables yielding significant differences in frequency distributions and mean scores were then used in a binary logistic regression model to calculate the probability of the occurrence of *HNF1B* mutations. Continuous variables were coded using age-related critical values. Results were considered significant if $p < 0.05$. All analyses were performed using IBM SPSS Statistics 22.

RESULTS

Using the selection criteria described in Table 1, we found *HNF1B* mutations in 10% of patients (n=20, 8.2% children and 14.3% adults). All reported cases were index cases. Data on patients with *HNF1B* mutations are summarized in Table 2. Comparison between clinical, laboratory and imaging characteristics in patients with and without *HNF1B* mutations is shown in Table 3 and 4. There were no significant differences in the presence of the antenatal diagnosis in the mutated and non-mutated groups.

Mutational analysis

The most frequent mutation was a heterozygous deletion of the *HNF1B* gene detected in 50% of cases. Other mutations were a duplication (1 patient – full gene duplication) or single base pair substitutions (6 – only 5 different – missense mutations, 1 nonsense (stop) mutation, 1 splice mutation and 1 frame shift mutation) (Table 2, Supplementary Table 1). We found no correlation between the types of mutation, the age of the diagnosis and the severity of renal phenotype or kidney function. Positive familial history of renal disease and/or diabetes and/or gout was found with similar frequency in patients with or without *HNF1B* mutations. Eight mutations were *de novo* (all full gene deletions), in 5 cases familial analysis was not available and in 7 cases the mutation was inherited. In these inherited cases, 57% of carrier parents were also affected and siblings were affected in 14% of these cases.

Renal anomalies

In line with results of the previous studies [8, 10, 12], in our cohort all patients having *HNF1B* mutations were diagnosed with bilateral renal abnormalities (Table 3). The most frequent major anomaly were cysts

from unknown origin, which were detected in 65%. The presence of two or more major renal criteria increased the risk to find *HNF1B* mutation by factor 2 (Figure 1). Interestingly, fetal "bright" hyper-echogenic kidneys described in other cohorts were not found in our *HNF1B*–mutated patients, while they were present in 5/185 of patients without *HNF1B* mutations: however, the information about fetal renal ultrasound was not available in all adult patients. Thus, isolated minor renal anomalies are rather predictive for the negative *HNF1B* analysis (p=0.05). Unexpectedly, hyperuricosemia reported in other cohorts was not predictive for finding HNF1B mutation and was present only in 4 of the *HNF1B*+ patients. The only biochemical parameter associated with *HNF1B* mutations was hypomagnesaemia found in 5/20 (25%) of the *HNF1B* positive patients compared to 5% of *HNF1B* negative patients (p=0.008) (Table 4). Although altered creatinine clearance was not predictive for finding *HNF1B* mutations, it was decreased (<90 ml/min/1.73 m2) in 8/12 children and in 5/8 adults. One patient underwent combined kidney-pancreas transplantation one year after diagnosis.

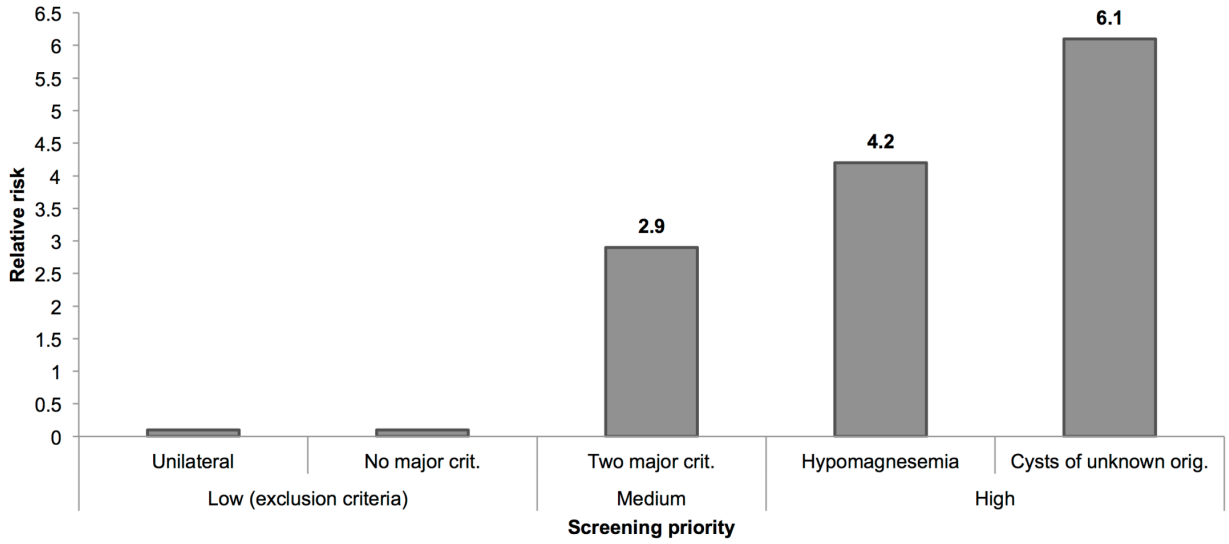
Extra-renal anomalies

Diabetes mellitus was diagnosed in 0/12 children and 5/8 adults having *HNF1B* mutations compared to 0/143 and 5/42 children and adults without a *HNF1B* mutation respectively, however, it was not predictive for finding the mutation. Liver enzyme abnormalities were detected in 2/12 and in 2/8 children and adults with *HNF1B* mutation, with the frequencies being comparable to not-mutated patients.

Relative risk for finding HNF1B mutations

Relative risk for finding *HNF1B* mutations was highest for patients having cysts from unknown origin (6.1 (95% CI [2.50, 15.01]; p<0.001) followed by hypomagnesaemia (4.2 (95% CI [1.78, 10.03]; p=0.001) and two different major criteria (2.9 (95% CI [1.29, 6,67]; p=0.010) (Figure 1).

FIGURE 1



DISCUSSION

The described phenotypic spectrum of CAKUT associated with *HNF1B* mutations is broad and encompasses renal cysts in patients typically having normal or decreased kidney size, solitary functioning kidneys, renal hypo/dysplasia, glomerulocystic disease, oligomeganephronia, hydronephrosis, pyeloureteral junction stenosis and VUR [8, 10, 13]. With the exception of patients carrying large deletions, no genotype-phenotype correlations have been demonstrated so far; even carriers of the same inherited mutation within one family can have different clinical presentations complicating the developing of screening criteria for the *HNF1B* mutational analysis. Because of the high prevalence (~10 to 30%) of *HNF1B* mutations found in different CAKUT cohorts [8, 10-13], this gene is analysed most frequently in CAKUT patients.

In our study, we used the criteria previously published in the literature. Ulinski et al. [10] tested children based on the presence of renal cysts, hyperechogenicity, hypoplasia or single kidney and found *HNF1B* mutations in 31%. The same criteria (with MCDK and hyperuricemic tubulointerstitial nephropathy in addition) were used by Heidet et al. [8] with a mutation detection rate of 20%. Decramer et al. [13] based their screening on the diagnosis of fetal bilateral hyperechogenic kidneys and found *HNF1B* mutations in 29% of the patients.

In our hospital, using the criteria mentioned above, *HNF1B* analysis was prospectively performed in 205 patients over a 3 years period and yielded 20 positive cases. The frequency of *HNF1B* mutations was slightly lower compared to previously published cohorts, most likely due to the prospective character of our study limiting the selection bias. Moreover, all cases reported in the current study were index cases using pre-defined clinical criteria, and the family members detected by the family screening were not included in the analysis, irrespectively whether they had CAKUT anomalies

The severity of renal and extra-renal phenotype did not differ significantly between paediatric and adult patients and there was no correlation between the type of the mutation, the age of the diagnosis and the creatinine clearance, although renal dysplasia was the most frequently renal anomaly in children and cysts of unknown origin in adults. This indicates that adult patients with well-defined phenotype fitting the screening criteria have to be rigorously tested for *HNF1B* mutations as this has direct medical consequences for the patients. In this regard, the high risk of post-transplant onset of diabetes mellitus in *HNF1B* positive patients should be carefully considered [18]. Furthermore, recently demonstrated association between HNF1B expression levels and certain types of cancers (ovarian, endometrial, prostate, liver) necessitates careful follow-up of these patients [2, 19-22]. Gynaecological examination and follow-up are recommended in females with *HNF1B* mutations, since uterine abnormalities are common (2 out of 3 adult female patients in our cohort had a uterine abnormality). Moreover, the dominant inheritance of the mutation should be taken into account for counselling of the families.

Interestingly, in our cohort of *HNF1B* mutated patients, we didn't had indications for overt pancreas dysfunctions, however, some mild subclinical anomalies cannot be excluded. For example, elastase deficiency can be present in the absence of clinical symptoms in patients with pancreas hypoplasia [23, 24].

Our study indicates that the number of screened patients can be reduced without missing cases (Figure 1). Based on our results, we propose to restrict *HNF1B* genetic analysis to patients having bilateral renal anomalies, in particular, renal dysplasia and cysts of unknown origin. A combination of two major renal anomalies increases the likelihood of finding the mutation by factor 2, and an associated hypomagnesaemia by factor 4. *HNF1B* analysis should be considered in all patients fitting these criteria

irrespectively of age at presentation, extra-renal symptoms or the presence of affected family members. Screening should be discouraged if there are isolated unilateral renal abnormalities or an absence of a major criterion. The use of these criteria in our cohort would reduce the amount of patients requiring genetic analysis by 50% without any missing cases. The incidence of *HNF1B* mutations would increase from 10% to 19% implicating a major reduction in screening costs.

Recently Faguer et al. [25] developed a 17-items score for selecting patients for *HNF1B* mutational analysis and tested it in a large cohort of 433 individuals containing 56 mutated cases. The score of ≤8 ruled out *HNF1B* mutations with a sensitivity of 98.2% and a specificity of 41.1%. We applied this score to our cohort and found that this would reduce the number of patients eligible for the screening to 55, but we would miss 3 out of 20 patients with *HNF1B* mutations (patients 7, 8, 10 in Table 2 and Supplementary Table 1). These patients lacked a clear family history, had bilateral dysplasia 'only' (patient 8 and 10) or dysplasia and agenesis (patient 7) without electrolyte abnormalities, cysts, pancreas abnormalities or other extra-renal manifestations which result in the Faguer-score with a maximum of 6 (while 8 was necessary for screening *HNF1B* in their cohort). In contrast, these patients would have been screened in our restricted protocol.

Interestingly, two patients (patients 7 and 10 in Table 2 and Supplementary Table 1) in our cohort having low Faguer's scores, had a missense mutation and one patient has a duplication of the HNF1B gene (patient 8). Based on in silico prediction tools (SIFT [26] and PolyPhen2 [27]), the conservation of the amino acid and the population frequency observed in different variant databases (dbSNP [28], ESP [29], GoNL [30], our in-house database (which consists of 384 unaffected and unrelated parents, unrelated oncology patients), the c.1640C>T (p.S547F) is considered to be likely pathogenic (Supplementary Table 1). There is some skepticism towards the pathogenicity of the variant c.226G>T (p.G76C), since this variant was observed in 2 unrelated families, but is also present at a frequency of 0.02% in the European American population [29, 31]. Segregation analysis in large families might shed light on the role of this variant. Concerning the third variant, the duplication of HNF1B, this is a rare event in comparison to the deletion of the complete HNF1B gene. Faguer et al. [32] also described a patient with a 17q12 chromosomal duplication, accompanying the HNF1B gene, associated with renal disease.

Our screening criteria compared to those of Faguer et al. are less specific, but are more applicable for routine clinical practice, where, for example prenatal history, information on pathological specimen of the kidney and full anatomical information on kidneys and/or pancreas are often lacking.

The spectrum of mutations found in our cohort was comparable to already published studies with *de novo* deletions being the most prevalent type of mutations [8, 25, 33, 34]. Interestingly, screening of the family members revealed 5/13 asymptomatic parents of the children and 2/7 asymptomatic parents of the adults pointing to the extreme phenotypic variability and questioning the pathogenicity of the mutations. However, among these cases 3/7 mutations have been previously reported in association with the clinical phenotype (Table 2) or were predicted being pathogenic by prediction programs.

The phenotypic variability in patients with *HNF1B* mutations is not fully understood. During mammalian kidney development, HNF-1β is expressed in the Wolffian duct and metanephric mesenchyme starting from the renal vesicle stage [35, 36]. Embryonic lethality of *Hnf1b* knock-out mouse model due to visceral endoderm defects hindered studying its regulatory role in nephrogenesis [37]. Subsequent strategies undertaken to overcome this problem revealed the pivotal role of the gene in ureteric bud branching involving Wnt9b signaling. Recent studies in zebra fish mesonephros identified Hnf1b as a major regulator of proximo-distal tubular segmentation [38]. Transcriptional targets of HNF1β in mice include several genes involved in renal cystic disease such as *Pkhd1, Pkd2, Pkd1, Umod, Inf88, Kif3a, TMEM27* [39-42], and prenatal Hnf1b inactivation in the developing kidney resulted in severe polycystic disease [42, 43]. Inducible inactivation of Hnf1b in mice after 10 days of birth didn't cause cystic lesions suggesting that cyst formation is linked to the morphogenetic proliferation [42]. Interestingly, when Hnf1b tubules were forced to regenerate by inducing ischemia-reperfusion injury, cyst formation could be stimulated even when the gene was inactivated after completed kidney development [42] signifying that the heterogeneity of HNF1b-associated phenotype might be related to the environmental factors stimulating tubular proliferation**.** In this respect, high prevalence of renal cysts found in our adult *HNF1B* positive patients (7/8) compared to 6/12 children, mostly having renal dysplasia, might support this pathogenic mechanism, however, to which extent the transcriptional network if Hnf1b in mice can be extended to humans still remains unclear.

The epigenetic regulation of HNF1β expression by microRNA's that has recently been demonstrated also points to the complexity of the regulatory up- and downstream pathways that can be potentially responsible for the diversity of the phenotype (15).

The explanation of hypomagnesaemia in patients with *HNF1B* mutations unravelled the role of HNF1β in transcription of genes involved in renal magnesium handling [12, 39, 44]. There are HNF1β binding sites in the *FXYD2* gene, encoding the γ-subunit of the Na(+)/K(+)-ATPase and mutations in this gene are linked to familial autosomal dominant isolated hypomagnesaemia [12] [45]. Interestingly, analysis of mRNA derived from urine of *HNF1B*+ patients showed no altered expression of *FXYD2*, while urinary excretion of *ATP1A1* mRNA encoding α1-subunit of the Na(+)/K(+)-ATPase was significantly decreased, although the limited availability of mRNA that could be extracted from the urine limited the possibility to analyse the various isoforms of these genes [37]. In our cohort, hypomagnesaemia was found in 5/20 of *HNF1B* positive patients (1 child and 4 adults), suggesting that it might be a later manifestation of the disease [7, 8, 12, 33].

Although UMOD gene causing familial juvenile hyperuricemic nephropathy (FJHN) and medullary cystic kidney disease (MCKD) belongs to the transcriptional network of *HNF1B* [46], the frequency of hyperuricemia was rather low in our cohort and didn't differ between *HNF1B* positive and *HNF1B* negative patients. This observation contrasting the results of the other studies [8, 12] might be explained by a small number of the patients and a relatively good kidney function even in adults. On the other hand, our findings indicate that normal serum uric acid levels do not exclude finding *HNF1B* mutations in individual patients.

In summary, we propose to restrict *HNF1B* genetic analysis to patients having bilateral major renal anomalies, and in particular cysts from unknown origin in combination with hypomagnesaemia. *HNF1B* analysis should be considered in all patients fitting these criteria irrespectively of age at presentation, extra-renal symptoms or the presence of affected family members. In awaiting widespread availability of CAKUTome screening platforms, the adapted criteria suggested by our single centre prospective study should be validated in larger cohorts of CAKUT patients.

DISCLOSURES

All authors declared no conflicts of interest.

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TABLES

Table 1: Criteria for inclusion

Major criteria	**Minor criteria**
Fetal bilateral hyperechogenic kidneys	Ectopic kidney
Multicystic dysplastic kidney	Vesico-ureteral reflux
Renal agenesis	Hydronephrosis
Hypoplastic or dysplastic kidneys	
Cysts from unknown origin	
Extrarenal criteria	**Positive familial history**
Diabetes mellitus	Abnormalities in kidney
Hypomagnesaemia	Abnormalities in urogenital tract
Hypokalemia	Gout
Hyperuricemia	Liver function abnormalities
Liver function abnormalities	Diabetes or exocrine pancreas dysfunction